Hindawi Publishing Corporation
ISRN Critical Care
Volume 2013, Article ID 219048, 6 pages
http://dx.doi.org/10.5402/2013/219048

Research Article

Predictors of Disseminated Intravascular Coagulation in Patients with Septic Shock

Diana J. Kelm,[1] Juan Carlos Valerio-Rojas,[2] Javier Cabello-Garza,[2] Ognjen Gajic,[1,2,3] and Rodrigo Cartin-Ceba[1,2,3]

[1] *Department of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA*
[2] *Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC), Rochester, MN 55905, USA*
[3] *Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, USA*

Correspondence should be addressed to Diana J. Kelm; kelm.diana@mayo.edu

Received 6 August 2013; Accepted 2 September 2013

Academic Editors: M. S. C. de Assuncao and N. Gibney

Purpose. The goal of this study was to identify potential clinical predictors for the development of disseminated intravascular coagulation (DIC) in patients with septic shock. *Material and Methods*. We performed a retrospective analysis of a cohort of adult (>18 years of age) patients with septic shock admitted to a medical ICU in a tertiary care hospital from July 2005 until September 2007. A multivariate logistic regression model was used to determine the association of risk factors with overt DIC. *Results*. In this study, a total of 390 patients with septic shock were analyzed, of whom 66 (17%) developed overt DIC. Hospital mortality was significantly greater in patients who developed overt DIC (68% versus 38%, $P < 0.001$). A delay in the timing of antibiotics was associated with an increased risk of the development of overt DIC ($P < 0.001$). Patients on antiplatelet therapy prior to hospital admission and who that received adequate early goal-directed therapy (EGDT) were associated with a decreased risk of overt DIC ($P < 0.001$). *Conclusions*. In our cohort of patients with septic shock, there was a risk reduction for overt DIC in patients on antiplatelet therapy and adequate EGDT, while there was an increased risk of DIC with antibiotic delay.

1. Introduction

Sepsis is the leading cause of mortality in noncardiac ICU admissions [1]. The reported incidence of septic shock ranges from 6.3% to 14.7% [2]. Based on the landmark study by Rivers et al., early aggressive resuscitation guided by continuous central venous oxygen saturation ($ScvO_2$), central venous pressure (CVP), and mean arterial pressure (MAP) monitoring reduced both in-hospital mortality rates from 56.8% to 42.3% and 28-day mortality rates from 46.5% to 30.5% [3]. Disseminated intravascular coagulation (DIC) is commonly seen in septic patients and is associated with an increased rate of morbidity and mortality [4].

DIC is defined by the International Society of Thrombosis and Hemostasis (ISTH) as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature. When sufficiently severe, it can produce organ dysfunction" [5]. In 2001, the DIC subcommittee of the ISTH developed a DIC score since it is essentially a clinical diagnosis based on laboratory assays, specifically low platelet count, elevated fibrin-related markers (soluble fibrin monomers or fibrin degradation products), elevated prothrombin time, and low fibrinogen level [5]. The diagnosis of overt DIC based on an ISTH DIC score ≥5 was found to be associated with high severity of disease and a fivefold increased risk of death [1], [6].

In DIC, there is a widespread formation of fibrin clots leading to microvascular occlusion and reduced oxygen delivery; if this is severe and prolonged, then organ dysfunction ensues [7, 8]. Patients with overt DIC had higher mortality than those without overt DIC, ranging from 43 to 48% [2, 6]. Despite the high mortality associated with DIC, there are no good clinical predictors of DIC; thus, we aimed to determine the risk factors associated with the development of DIC in patients with septic shock treated with early goal-directed therapy (EGDT).

2. Materials and Methods

This study was approved by the Mayo Clinic Institutional Review Board. Informed consent was not necessary as this was a minimal risk study. We performed a retrospective analysis of a prospectively assembled cohort of consecutive adult (>18 years of age) patients with septic shock admitted to a medical ICU in a tertiary care hospital from July 2005 until September 2007. Exclusion criteria included those with a preexisting diagnosis of DIC, lack of research authorization, patients in whom care was withdrawn within six hours of onset of septic shock, readmissions, or those transferred from an outside facility. Data was extracted through chart review. A similar study design was conducted by Plataki and colleagues [9].

The diagnosis of septic shock was based on the guidelines defined by the American College of Chest Physicians and Society of Critical Care Medicine. The following were required on two consecutive measurements in a patient with suspected infection: two systemic inflammatory response syndrome (SIRS) criteria (temperature > 38.3°C or <35.6°C, heart rate > 90 beats/min, respiratory rate > 20/min, or white blood cell count > 12.0×10^3 or $<4.0 \times 10^3$) and hypoperfusion (systolic blood pressure ≤ 90 mmHg or MAP ≤ 60 mmHg or a fall of >40 mmHg from baseline) despite a 20 mL/kg fluid bolus or serum lactate ≥ 4 mmol/L regardless of the blood pressure [10].

The development of DIC was based on a modified DIC scoring system from the ISTH [5, 6]. A score of ≥5 indicated overt DIC. The score was based on platelet count (>100 × 10^9/L = 0, <100 × 10^9/L = 1, and <50 × 10^9/L = 2), fibrinogen level (>100 mg/dL = 0, <100 mg/dL = 1), prothrombin time (<15 sec = 0, >15 sec = 1, >18 sec = 2), and d-dimer (<301 ng/mL = 0, >301 ng/mL = 1, >400 ng/mL = 2). The following methods were used for the measurement of fibrinogen, prothrombin, and d-dimer, respectively: STA Fibrinogen Kit, STA-R Evolution, and automated latex immunoassay. Labs were obtained when there was concern for DIC such as in a patient with new onset bleeding or thrombocytopenia.

Two authors (JVR and JCG) reviewed monitoring logs capturing various vital signs, laboratory findings, infusions, and other treatments to determine the time when criteria for septic shock and for DIC (if present) were met. Risk factors for the development of DIC were grouped as follows.

Patient's Underlying Health Condition prior to Admission. Patient demographics, comorbidities (preexisting diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, and end-stage renal disease), and outpatient medications (antiplatelet therapy, nonsteroidal anti-inflammatories, anticoagulants, statins, and chronic steroid use).

Physiologic and Laboratory Values at the Time of Diagnosis of Septic Shock. Vital signs, standard laboratory parameters, lactate, platelet count, fibrinogen level, prothrombin time, d-dimer, arterial blood gas measurements, acute physiologic and chronic health evaluation (APACHE) III scores, and need for mechanical ventilation and hemodynamic parameters when available.

EGDT (within the First Six Hours after Diagnosis of Septic Shock) and Interventions Assessment. Goal-directed fluid resuscitation, source control, time to antibiotic administration, use of vasopressors, steroid administration, transfusion of blood products, and use of activated protein C.

Adequate EGDT was defined as $ScvO_2$ ≥ 70%, CVP ≥ 8 mmHg, MAP ≥ 65 mmHg, urine output ≥0.5 mL/kg/hour, and/or improvement in lactate [3]. If resuscitation goals were not achieved within six hours, then this was considered a delay in EGDT. Adequate antibiotic therapy was defined as empiric broad spectrum antibiotics that would cover gram positives, gram negatives, and anaerobes according to the suspected site of infection [11]; in those with positive cultures, confirmation of adequate coverage was based on the specific organisms susceptibilities. If antibiotic administration was more than 3 hours after the onset of septic shock or there was resistance to the antibiotics initiated in the antibiogram of available positive cultures, these were considered as delayed antibiotic therapy.

The main outcomes measured were the development of DIC; secondary outcomes were in-hospital mortality and hospital and ICU length of stay (LOS). A univariate followed by a multivariate analysis was conducted to determine risk factors and outcomes between patients who did and did not develop DIC. Continuous data are described as medians (interquartile range, IQR) or means (standard deviation), as appropriate for non-parametric or parametric data, respectively. Categorical data are presented as counts with percentages. To test the difference in medians between groups, a Wilcoxon rank sum was used. Either Fisher's exact test or chi-squared test was used to note the differences in proportions where appropriate. Consideration for multivariable logistic regression models was based on the following: variables occurred before the development of DIC, had less than 10% missing data, P values < 0.1 in the univariate analysis, and were clinically plausible.

The final model was determined using both statistical and clinical criteria taking into consideration colinearity, interaction, and the number of patients who experienced the outcome of interest. Based on the forward selection process, a variable with a "stronger" association, in the case of colinearity, was used in multivariate analysis. The predictive accuracy of the multivariate model is reported as the area under the curve. The odds ratio (OR) and 95% confidence intervals (CI) were calculated; P values of <0.05 were considered statistically significant. JMP statistical software (version 8.0, SAS institute, Cary, NC) was used for all analyses.

3. Results

We identified 763 individuals with septic shock out of a total of 4893 consecutive admissions, of which 390 patients met the inclusion criteria (Figure 1). Sixty-six patients out of the 390 included in this study (17%) developed overt DIC based on the modified ISTH DIC score.

Table 1 presents univariate comparisons of baseline characteristics, including patient demographics, comorbidities, and medications, physiologic parameters, laboratory values at time of diagnosis of septic shock between those who

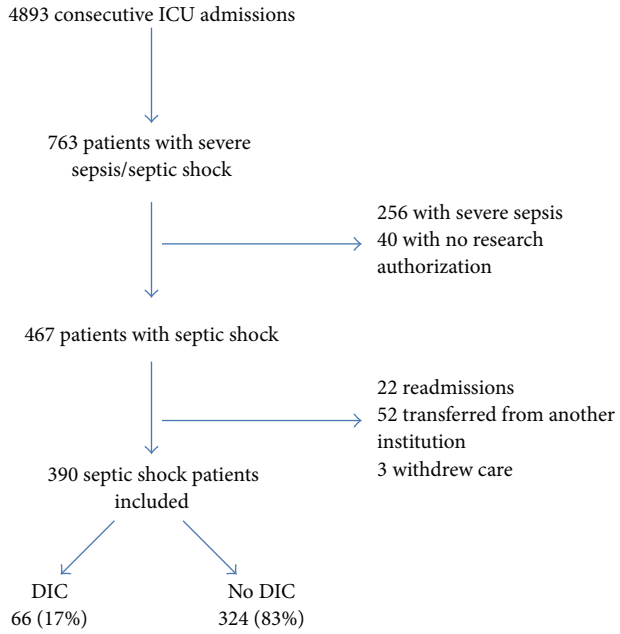

Figure 1

developed DIC and those who did not. The cohort of patients with DIC presented with a median (IQR) age of 63 (54–74) of which 56% were males and 83% were Caucasians. Those who developed DIC were slightly younger in age, more likely to have positive blood cultures, and less likely to be on aspirin, but not clopidogrel. Additionally, those who developed DIC were more severely ill, as indicated by higher APACHE III scores, cardiovascular sequential organ failure assessment (SOFA) scores, lactate levels, bicarbonate, and increased administration of steroids. Adequate early goal-directed resuscitation and adequate antibiotic therapy were more frequently achieved in the non-DIC patients (Table 1). During the time course of this study, activated protein C was still available although the use was limited at our institution due to staff bias. The hospital mortality was 68% for DIC patients versus 38% in non-DIC patients ($P < 0.001$) (Table 2). The ICU LOS was noted to be longer in the DIC patients, but this was not found to be statistically significant.

After adjusting for important confounders including baseline comorbidities and severity of disease, adequate resuscitation (OR 0.14 [95% CI, 0.06–0.29] $P < 0.001$) and prior use of antiplatelet therapy (OR 0.2 [95% CI, 0.08–0.44] $P < 0.001$) were independently associated with the reduction of risk for the development of overt DIC (Table 3). Additionally, our results found that, with every hour delay to adequate antibiotic use, there was an increase of 7% in the development of overt DIC (OR 1.07 [95% CI, 1.03–1.12] $P < 0.001$).

4. Discussion

In the present study, almost one of every five patients with septic shock who received EGDT developed overt DIC. The prehospitalization use of antiplatelet therapies, specifically aspirin and adequate EDGT, was associated with a reduced risk of overt DIC, while a delay in antibiotic administration was associated with an increased risk. Although no causation can be drawn from this study, this association is hypothesis generating, and several potential explanations could be implicated. To the best of our knowledge, our study is among the first to evaluate clinical predictors for the development of overt DIC in septic shock patients treated with EGDT.

There have been numerous studies evaluating the benefit of the pre-hospitalization use of antiplatelet drugs (aspirin and clopidogrel) in critically ill patients. Recently, a large study of 7945 ICU patients with SIRS and sepsis found that the use of low-dose aspirin (100 mg/day) was associated with lower mortality even when matched for independent variables [12]. The use of aspirin for at least six months prior to hospital admission led to shorter hospital stays and lower probability for the need for ICU treatment with associated lower SOFA scores indicating less organ dysfunction [13]. Other potential benefits of antiplatelet therapy in critically ill patients include a reduction in acute lung injury [14] and a lower risk of *Staphylococcus aureus* bacteremia in hemodialysis patients [15]. Not only pre-hospitalization aspirin therapy has been studied, but also one study analyzed 886 septic patients and found that those treated with aspirin during their ICU stay had significantly lower ICU and hospital mortality with an odds ratio of 0.56 and 0.57, respectively [16].

The reason for the potential reduction of the development of DIC by antiplatelet therapy may be found in the similarities between the mechanisms of action of the antiplatelet drugs and the pathophysiology of platelet activation during DIC. The activation of platelets is a multifactorial process and is crucial for normal hemostasis; however, it can also lead to platelet-rich thrombi as seen in atherosclerotic disease. Upon cell activation, platelets secrete tissue factor (TF) from granules [17] although there is now some controversy over this [18]; platelets may instead absorb TF and become carriers rather than secretors of TF. Nonetheless, TF and thrombin-mediated formation of fibrin from fibrinogen activate and recruit platelets, which can then lead to the generation of thrombus [19]. Antiplatelet therapy inhibits platelets by either irreversible inhibition of COX-1 which then blocks thromboxane A2 production, a potent stimulator of platelet aggregation (aspirin) or via inhibition of platelet activation induced by adenosine diphosphate (clopidogrel) [19].

Additionally, our study showed that both EGDT and early use of antibiotics led to a reduction in the development of DIC though we cannot say there is a causational association. There are numerous causes of DIC such as sepsis, malignancy, and trauma, which are able to induce systemic activation of coagulation either by causing release of procoagulant substances or by activating cytokines as part of the systemic inflammatory response as in sepsis [20]. Adequate fluid resuscitation and early antibiotic initiation have been shown to be beneficial in patients with septic shock. The Surviving Sepsis Campaign recommends aggressive fluid resuscitation within the first six hours of presentation [21]. In one study, there was 79.9% survival to hospital discharge when antibiotics are administered within the first hour of hypotension, and with each hour of delay in initiation of antibiotics there was a mean decrease in survival of 7.6% [11]. Thus, it appears that early

Table 1: Baseline demographics, physiologic and laboratory values at the time of diagnosis of septic shock and early goal-directed therapy, and interventions assessment.

	No DIC 324 (83%)	DIC 66 (17%)	*P* value
Baseline Demographics			
Age, years, median (IQR)	69 (57–80)	63 (54–74)	0.01
Male gender, *n* (%)	173 (53)	37 (56)	0.78
Caucasian, *n* (%)	295 (91)	55 (83)	0.07
Coronary artery disease, *n* (%)	97 (30)	19 (29)	0.68
Cerebrovascular disease, *n* (%)	44 (14)	8 (12)	0.78
Hypertension, *n* (%)	182 (56)	35 (53)	0.68
Diabetes mellitus, *n* (%)	94 (29)	17 (26)	0.65
End-stage renal disease, *n* (%)	25 (8)	7 (11)	0.45
Congestive heart failure, *n* (%)	99 (31)	13 (20)	0.09
Positive blood cultures, *n* (%)	54 (17)	22 (33)	0.003
Medications			
Antiplatelet therapy, *n* (%)	135 (42)	10 (15)	<0.001
Clopidogrel, *n* (%)	35 (11)	2 (3)	0.06
Aspirin, *n* (%)	114 (35)	9 (14)	<0.001
Warfarin, *n* (%)	22 (7)	4 (6)	0.99
Prophylactic subcutaneous heparin, *n* (%)	137 (42)	19 (29)	0.04
Chronic steroid use, *n* (%)	63 (19)	12 (18)	0.99
Physiologic Markers			
Acute physiology score, median (IQR)	68 (50–85)	84 (66–120)	<0.001
APACHE III, median (IQR)	84 (67–102)	96 (79–135)	<0.001
CV SOFA, median (IQR)	3 (3-4)	4 (3-4)	0.001
Predicted hospital death, % median (IQR)	37 (19–62)	58 (31–80)	<0.001
MAP mmHg, median (IQR)	56 (51–60)	55 (49–60)	0.31
Heart rate bpm, median (IQR)	97 (80–111)	103 (88–117)	0.02
Respiratory rate, median (IQR)	21 (18–26)	22 (19–27)	0.38
Laboratory Values			
Lactate mg/dL, median (IQR)	1.8 (1–1.31)	2.9 (1.5–5.9)	<0.001
Bicarbonate mmol/L, median (IQR)	20 (17–25)	17 (13–21)	<0.001
Platelet count per mm^3, median (IQR)	225 (158–310)	197 (148–284)	0.08
WBC count per mm^3, median (IQR)	13.7 (9.3–20)	12 (6.4–22)	0.14
EGDT Assessment			
Adequate resuscitation	177 (57)	12 (18)	<0.001
Time to adequate empiric antibiotics hours, median (IQR)	1.3 (0–4)	5.6 (1–12)	<0.001
Duration of hypotension minutes, median (IQR)	15 (11–60)	60 (15–120)	<0.001
Time to source control hours, median (IQR)	11.3 (5–27)	21 (5–36)	0.44
Steroids, *n* (%)	181 (56)	55 (83)	<0.001
Activated protein C, *n* (%)	17 (5.3)	9 (13.6)	0.02

aggressive resuscitation and early use of antibiotics decrease the mortality from septic shock, which could then also reduce the risk for the development of DIC.

Another important modulator of coagulation and inflammation seen often in severe sepsis is APC, which is an endogenous protein that inhibits thrombosis and inflammation and facilities fibrinolysis [22]. Inflammatory cytokines downregulate thrombomodulin, which impairs the conversion to APC [23]. In the majority of septic patients, there are reduced levels of protein C which has been associated with an increased risk of death [24]. The initial Prowess study found that the use of drotrecogin alpha activated led to a reduction in mortality at

Table 2: Main outcomes.

	No DIC 324 (83%)	DIC 66 (17%)	*P* value
Hospital mortality, *n* (%)	122 (38)	45 (68)	<0.001
Hospital LOS days, median (IQR)	9.3 (4.8–17.3)	8 (4–16.7)	0.24
ICU LOS days, median (IQR)	3.6 (1.7–7.2)	4.6 (2–8.3)	0.28

Table 3: Multivariate analysis, risk factors for the development of DIC in patients with septic shock.

	Odds ratio	95% CI	*P* value
Age (years)	0.98	0.96–1	0.19
Positive blood cultures	1.65	0.74–3.58	0.20
Antiplatelet therapy	0.20	0.08–0.44	<0.001
Predicted hospital mortality—APACHE	4.31	1.33–14.4	0.01
Adequate resuscitation	0.14	0.06–0.29	<0.001
Time to antibiotics (hours)	1.07	1.03–1.12	<0.001

28 days in patients with severe sepsis, relative risk reduction of 19.4%, and absolution reduction of 6.1% [25]. Another study was conducted from the Prowess database that looked at a subset of patients who were classified to have overt DIC based on the ISTH scoring system, which found that the use of drotrecogin alpha activated resulted in a relative risk reduction in mortality of 29.1% as compared to 18.5% in those without overt DIC. However, further studies have shown an increased harm, specifically increased risk of bleeding [26]. Again, the use of APC was limited in this cohort due to staff bias and is now off the market.

The limitations of this study arise from the inherent biases of a retrospective observational design. With this, our study only included overt DIC as based on the modified ISTH DIC score because labs were only obtained when there was concern for DIC, which could have allowed for milder DIC cases to be missed. Confounding factors, such as liver disease, inflammation, bone marrow suppression, drug-induced thrombocytopenia [27], specifically antibiotics, and hemodilution from fluid resuscitation, could contribute to a falsely elevated DIC score by inappropriate elevations in prothrombin and d-dimer and reductions in platelet count.

In conclusion, we explored both patient (pre-hospitalization use of antiplatelet therapy, specifically aspirin) and health care delivery (successful resuscitation and appropriate antibiotic administration) risk factors for the development of DIC in a contemporary cohort of patients with septic shock, and both seemed to be important. Health care delivery factors may be potentially modified, thus contributing to the reduction of DIC in patients with septic shock. The reduced risk of DIC with the use of aspirin requires additional confirmatory studies, but could be a potential intervention in the prevention of DIC.

Conflict of Interests

The author(s) declare(s) that there is no conflict of interests regarding the publication of this paper.

References

[1] M. S. Rangel-Frausto, D. Pittet, M. Costigan, T. Hwang, C. S. Davis, and R. P. Wenzel, "The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study," *The Journal of the American Medical Association*, vol. 273, no. 2, pp. 117–123, 1995.

[2] M. Antonelli, M. Levy, P. J. D. Andrews et al., "Hemodynamic monitoring in shock and implications for management," *Intensive Care Medicine*, vol. 33, no. 4, pp. 575–590, 2007.

[3] E. Rivers, B. Nguyen, S. Havstad et al., "Early goal-directed therapy in the treatment of severe sepsis and septic shock," *The New England Journal of Medicine*, vol. 345, no. 19, pp. 1368–1377, 2001.

[4] J. Kramer, H. M. Otten, M. Levi, and H. T. Cate, "The association of disseminated intravascular coagulation with specific diseases," *Reanimation*, vol. 11, no. 8, pp. 575–583, 2002.

[5] F. B. Taylor, C. H. Toh, W. K. Hoots, H. Wada, and M. Levi, "Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation: on behalf of the scientific subcommittee on disseminated intravascular coagulation (DIC) of the international society on thrombosis and haematostasis (ISTH)," *Thrombosis and Haemostasis*, vol. 86, no. 5, pp. 1327–1330, 2001.

[6] C. Voves, W. A. Wuillemin, and S. Zeerleder, "International society on thrombosis and haemostasis score for overt disseminated intravascular coagulation predicts organ dysfunction and fatality in sepsis patients," *Blood Coagulation and Fibrinolysis*, vol. 17, no. 6, pp. 445–451, 2006.

[7] S. Zeerleder, C. E. Hack, and W. A. Wuillemin, "Disseminated intravascular coagulation in sepsis," *Chest*, vol. 128, no. 4, pp. 2864–2875, 2005.

[8] S. Gando, "Microvascular thrombosis and multiple organ dysfunction syndrome," *Critical Care Medicine*, vol. 38, no. 2, pp. S35–S42, 2010.

[9] M. Plataki, K. Kashani, J. Cabello-Garza et al., "Predictors of acute kidney injury in septic shock patients: an observational cohort study," *Clinical Journal of the American Society of Nephrology*, vol. 6, no. 7, pp. 1744–1751, 2011.

[10] "American college of chest physicians/society of critical care medicine consensus conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis," *Critical Care Medicine*, vol. 20, no. 6, pp. 864–874, 1992.

[11] A. Kumar, D. Roberts, K. E. Wood et al., "Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock," *Critical Care Medicine*, vol. 34, no. 6, pp. 1589–1596, 2006.

[12] D. P. Eisen, "Manifold beneficial effects of acetyl salicylic acid and nonsteroidal anti-inflammatory drugs on sepsis," *Intensive Care Medicine*, vol. 38, no. 8, pp. 1249–1257, 2012.

[13] J. Winning, J. Reichel, Y. Eisenhut et al., "Anti-platelet drugs and outcome in severe infection: clinical impact and underlying mechanisms," *Platelets*, vol. 20, no. 1, pp. 50–57, 2009.

[14] D. J. Kor, J. Erlich, M. N. Gong et al., "Association of prehospital-ization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients," *Critical Care Medicine*, vol. 39, no. 11, pp. 2393–2400, 2011.

[15] M. Sedlacek, J. M. Gemery, A. L. Cheung, A. S. Bayer, and B. D. Remillard, "Aspirin treatment is associated with a significantly decreased risk of *Staphylococcus aureus* bacteremia in hemodialysis patients with tunneled catheters," *The American Journal of Kidney Diseases*, vol. 49, no. 3, pp. 401–408, 2007.

[16] G. P. Otto, M. Sossdorf, J. Boettel et al., "Effects of low-dose acetylsalicylic acid and atherosclerotic vascular diseases on the outcome in patients with severe sepsis or septic shock," *Platelets*, vol. 24, no. 6, pp. 480–485, 2013.

[17] S. H. Slofstra, C. A. Spek, and H. T. Cate, "Disseminated intravascular coagulation," *Hematology Journal*, vol. 4, no. 5, pp. 295–302, 2003.

[18] B. Østerud and J. O. Olsen, "Human platelets do not express tissue factor," *Thrombosis Research*, vol. 132, no. 1, pp. 115–114, 2013.

[19] L. K. Jennings, "Mechanisms of platelet activation: need for new strategies to protect against platelet-mediated atherothrombosis," *Thrombosis and Haemostasis*, vol. 102, no. 2, pp. 248–257, 2009.

[20] M. Levi, C. H. Toh, J. Thachil, and H. G. Watson, "Guidelines for the diagnosis and management of disseminated intravascular coagulation," *The British Journal of Haematology*, vol. 145, no. 1, pp. 24–33, 2009.

[21] R. P. Dellinger, M. M. Levy, A. Rhodes et al., "Surviving sepsis campaign," *Critical Care Medicine*, vol. 41, no. 2, pp. 580–637, 2013.

[22] C. T. Esmon, "The protein C anticoagulant pathway," *Arteriosclerosis and Thrombosis*, vol. 12, no. 2, pp. 135–145, 1992.

[23] M. W. J. Boehme, Y. Deng, U. Raeth et al., "Release of thrombomodulin from endothelial cells by concerted action of TNF-α and neutrophils: in vivo and in vitro studies," *Immunology*, vol. 87, no. 1, pp. 134–140, 1996.

[24] J. A. Lorente, L. J. Garcia-Frade, L. Landin et al., "Time course of hemostatic abnormalities in sepsis and its relation to outcome," *Chest*, vol. 103, no. 5, pp. 1536–1542, 1993.

[25] G. R. Bernard, J. Vincent, P. Laterre et al., "Efficacy and safety of recombinant human activated protein C for severe sepsis," *The New England Journal of Medicine*, vol. 344, no. 10, pp. 699–709, 2001.

[26] A. J. Martí-Carvajal, I. Solà, D. Lathyris, and A. F. Cardona, "Human recombinant activated protein C for severe sepsis," *Cochrane Database of Systematic Reviews*, vol. 12, Article ID CD004388, 2012.

[27] J. L. Priziola, M. A. Smythe, and W. E. Dager, "Drug-induced thrombocytopenia in critically ill patients," *Critical Care Medicine*, vol. 38, no. 6, pp. S145–S154, 2010.